A 24-Week Open-Label Extension Study of Olanzapine-Fluoxetine Combination and Olanzapine Monotherapy in the Treatment of Bipolar Depression

Sara A. Corya, M.D.; Roy H. Perlis, M.D.; Paul E. Keck, Jr., M.D.; Daniel Y. Lin, Ph.D.; Michael G. Case, M.S.; Doug J. Williamson, M.B.Ch.B., M.R.C.Psych.; and Mauricio F. Tohen, M.D., Dr.P.H.

Objective: Olanzapine-fluoxetine combination has shown efficacy in the acute treatment of depressive episodes in patients with bipolar I disorder. The present analyses examined the efficacy and safety of longer term treatment with olanzapine-fluoxetine combination or olanzapine monotherapy in a 6-month open-label extension study.

Method: 376 patients with DSM-IV bipolar I disorder, depressed, who completed an acute trial entered the open-label study and received 1 week of olanzapine monotherapy (5–20 mg/day). At all subsequent visits, patients could choose between olanzapine monotherapy or olanzapine-fluoxetine combination (6/25, 6/50, or 12/50 mg/day). Three treatment groups were defined retrospectively according to the medication course taken from week 1: olanzapine, olanzapine-fluoxetine combination, or switched. The efficacy measures were the Montgomery-Asberg Depression Rating Scale (MADRS), Clinical Global Impressions-Bipolar Version, and Young Mania Rating Scale. The study was conducted from July 2000 to May 2002.

Results: Among patients who started in remission, MADRS total scores did not change significantly from baseline to endpoint in the olanzapine-fluoxetine combination (0.8) or olanzapine (0.3) groups, but increased slightly in the switched (2.3, p = .02) group. For patients who started in nonremission, MADRS total scores decreased significantly in all groups (olanzapine-fluoxetine combination: –5.7, p = .001; olanzapine: –11.6, p = .004; switched: –6.4, p = .015). The majority of patients who entered the study in nonremission achieved remission (MADRS total score ≤ 12) during the trial (olanzapine-fluoxetine combination: 66.7%, olanzapine: 64.7%, switched: 62.5%). The overall rate of depressive relapse was 27.4%, and the overall incidence of mania emergence was 5.9%.

Conclusions: The present findings suggest that long-term treatment with olanzapine-fluoxetine combination may be a useful option for the management of depressive symptoms and carries a low risk of mania emergence.

(J Clin Psychiatry 2006;67:798–806)

Received March 22, 2005; accepted Jan. 30, 2006. *From Lilly Research Laboratories, Indianapolis, Ind. (Drs. Corya, Lin, Williamson, and Tohen and Mr. Case); the Department of Psychiatry, Harvard Medical School/McLean Hospital, Belmont, Mass. (Drs. Perlis and Tohen); and the Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio (Dr. Keck).*

This work was sponsored by Eli Lilly and Company.

Drs. Corya, Lin, Williamson, and Tohen and Mr. Case are employees of Eli Lilly and Company; Dr. Perlis has served as a consultant, speaker, or advisory board member for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, and Pfizer; and Dr. Keck is a consultant to or member of the scientific advisory boards of Abbott, AstraZeneca, Bristol-Myers Squibb, Corcept, GlaxoSmithKline, Janssen, Eli Lilly, Novartis, Ortho-McNeil, Pfizer, UCB Pharma, Shire, and Wyeth and is a principal or co-investigator on research studies sponsored by Abbott, the American Diabetes Association, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Elan, Eli Lilly, Janssen, Merck, National Institute of Mental Health, National Institute of Drug Abuse, Organon, Ortho-McNeil, Pfizer, the Stanley Medical Research Institute, and UCB Pharma.

Corresponding author and reprints: Sara A. Corya, M.D., Eli Lilly and Co., Lilly Corporate Center, Indianapolis, IN 46285 (e-mail: corya_sara_a@lilly.com).

Bipolar I disorder is a serious recurring illness that affects approximately 1.6% of the adult population in the United States.[1,2] Treatments for the depressive phase of bipolar disorder have historically received less attention than those for mania, yet recent studies have highlighted the need for more effective management strategies from medical, social, and economic perspectives. Patients with bipolar I disorder experience depressive symptoms over 3 times longer than they do manic symptoms, and depression is the most common reason given for seeking medical treatment.[3] Recovery from a depressive episode also takes longer than from a manic episode, with a median time of 9 weeks versus 5 weeks, respectively.[4] The burden of illness associated with bipolar depression is particularly severe, with a greater risk of suicide and poor psychosocial functioning.[5,6] Dilsaver et al.[7] reported that the relative risk of suicide among patients with bipolar depression was 34.9 times greater than that among patients with pure mania. According to recent cost analyses, the economic burden associated with the management of patients with bipolar depression is also greater relative to that for patients with pure mania.[8,9]

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Despite the clear medical need and public health implications, the options available for treatment of bipolar depression remain more limited than those for mania. In the past, common treatments have included antidepressant monotherapy or adjunctive use of mood stabilizers with antidepressants. Recent findings indicate that antidepressant monotherapy is less effective than an antidepressant/mood stabilizer combination and may also lead to a deterioration of the illness course.[10] The use of antidepressant monotherapy in bipolar depressed patients, particularly tricyclic antidepressants, has been associated with an increased risk of inducing mania or hypomania, or accelerating cycling of mood episodes.[11,12]

Olanzapine is an atypical antipsychotic drug that has demonstrated efficacy for the treatment of acute manic episodes and for long-term maintenance treatment to delay relapse in patients with bipolar I disorder.[13,14] In an 8-week, randomized, double-blind, placebo-controlled study, olanzapine-fluoxetine combination was shown to be effective for the treatment of acute depressive episodes in patients with bipolar I disorder.[14] The magnitude of the decrease in depressive symptomatology was greater with olanzapine-fluoxetine combination relative to both olanzapine monotherapy and placebo. Notably, the effects of olanzapine-fluoxetine combination were clearly differentiated from placebo as early as 1 week after initiation of therapy, and the combination treatment was associated with greater response and remission rates at the end of the 8-week study.

The present study is a 24-week open-label extension of the aforementioned acute trial[14] in bipolar I patients who initially presented with a bipolar depressive episode. The objective of this study was to provide additional information to characterize the long-term efficacy and safety of olanzapine-fluoxetine combination and olanzapine monotherapy in these patients.

METHOD

Patients

Patients 18 years or older entered this 24-week extension study immediately after completion of the 8-week acute study.[14] At entry into the acute study, patients were required to have a diagnosis of bipolar I disorder with a current major depressive episode as confirmed by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Patient Version (SCID).[15] Patients were required to have a Montgomery-Asberg Depression Rating Scale (MADRS)[16] total score of at least 20 and a history of at least 1 previous manic or mixed episode of sufficient severity to require treatment with a mood stabilizer or an antipsychotic agent. At randomization in this acute study, subjects were allocated to the placebo, olanzapine monotherapy, or olanzapine-fluoxetine combination treatment groups in a 4:4:1 proportion.[14] Exclusion criteria included a history of alcohol or substance dependence within the previous 3 months, suicidal behavior within the previous 3 months, or an unstable or untreated medical disorder.

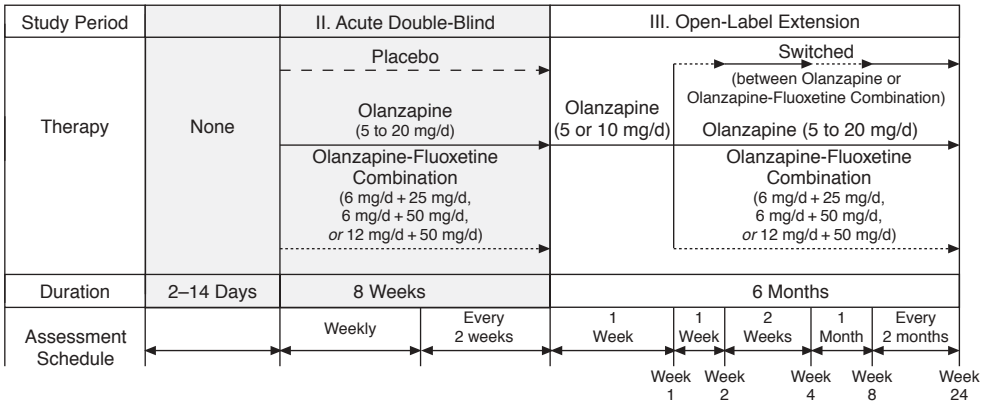
To enter the extension phase of the study, patients had to complete the 8-week acute study. Two populations of patients were defined according to their symptomatic status at the last visit in the acute phase of the study. Patients with a MADRS total score ≤ 12 were defined as remitters, while those with a MADRS total score > 12 were defined as nonremitters. Some patients were allowed to enter the open-label phase prior to completion of all 8 weeks of the acute study, due to lack of response or a worsening of symptoms. These patients are not included in the efficacy analyses, but are included in the safety analyses. The study was conducted from July 2000 to May 2002.

Procedure

A diagram summarizing the study phases and possible treatment courses is presented in Figure 1. All patients received olanzapine 5 or 10 mg/day during the first week of the open-label extension study, regardless of previous double-blind treatment assignment. Thereafter, the dose of olanzapine could have ranged from 5 to 20 mg/day. After the first week and at each subsequent visit during the extension study, patients could be switched to olanzapine-fluoxetine combination 6/25, olanzapine-fluoxetine combination 6/50, or olanzapine-fluoxetine combination 12/50. Based on the clinical judgment of the investigator, treatment could be switched at any visit between olanzapine monotherapy and olanzapine-fluoxetine combination during the 6-month open-label phase, as long as the change occurred at scheduled visits. Three treatment arms were defined retrospectively based on the medication course taken during the open-label extension study: (1) "olanzapine-fluoxetine combination" patients received olanzapine monotherapy during the first week (as required by the study protocol), switched to olanzapine-fluoxetine combination at the end of the first week (week 1), and stayed with the combination for the remainder of the open-label phase; (2) "olanzapine" patients continued on olanzapine monotherapy exclusively for the duration of their participation in the study; and (3) "switched" patients received olanzapine monotherapy during the first week (again, as defined by the study protocol) and either switched to olanzapine-fluoxetine combination at the end of the first week and then switched back to olanzapine at a later time, or stayed on olanzapine monotherapy after the first week and switched to olanzapine-fluoxetine combination at a later time in the open-label phase. Some patients switched treatments multiple times.

Patients were permitted adjunctive use of benzodiazepines (up to 2 mg of lorazepam equivalents per day) throughout the study. Anticholinergic therapy (benztropine mesylate or biperiden, ≤ 6 mg/day, or trihexyphen-

Figure 1. Study Design



idyl, ≤ 12 mg/day) for treatment of extrapyramidal symptoms, but not for prophylaxis, was permitted throughout the study. Concomitant use of other psychotropic medications was not permitted during the extension study.

Assessments

Severity of symptoms was assessed with the MADRS,[16] the severity of illness rating from the Clinical Global Impressions scale for Bipolar Disorder (CGI-BP),[17] and the 11-item Young Mania Rating Scale (YMRS).[18] These assessments were administered at weeks 1, 2, 4, 8, 12, and 24 of the open-label extension period. The categorical definitions included the following: *Remission* was defined a priori as a MADRS total score ≤ 12 at any time during the trial, and time to remission was determined on the basis of when the patient first satisfied that criteria. *Relapse into an affective episode* was defined a priori as a YMRS ≥ 15 (mania) or MADRS total score ≥ 16 (depression) in a patient who previously met the criteria for remission at baseline. Time to depressive relapse was assessed by prospectively examining the data for patients who satisfied the criteria for remission from the prior acute depressive episode at week 1 of the open-label phase.

Safety was monitored by assessing adverse events, laboratory values, electrocardiograms (ECGs), vital signs, weight change, and extrapyramidal symptoms measured with the Simpson-Angus Rating Scale[19] and Abnormal Involuntary Movement Scale (AIMS).[20] Adverse events or abnormal values that occurred or were exacerbated during the open-label trial were considered treatment-emergent. Potentially clinically significant increases in nonfasting glucose were defined as values ≥ 200 mg/dL in patients who had values less than 200 mg/dL during the preceding 8 weeks. Instances of treatment-emergent change in nonfasting total cholesterol were defined as values ≥ 240 mg/dL at any time during the open-label trial in patients who had values ≤ 200 mg/dL during the preceding 8-week acute trial.

Statistical Analysis

Analyses of treatment effectiveness included data from a subset of patients who completed the double-blind acute phase of the trial, completed the required 1-week treatment with open-label olanzapine, did not change categorical remission status during that week, and had at least 1 subsequent visit during which clinical assessments were recorded. Scores on the primary efficacy scale, the MADRS, were analyzed using a mixed-model repeated measures (MMRM), which included terms for baseline, investigator, therapy, visit, and visit × therapy interaction. Scores on the secondary efficacy scales (CGI-BP and YMRS) were analyzed using a last-observation-carried-forward (LOCF) methodology. Continuous safety measures were also analyzed using LOCF. Kaplan-Meier methodology was used to estimate the cumulative probability of remission by time among patients who entered the open-label extension study with a nonremission status. The same methodology was used to estimate the probability of relapse to a depressive episode in patients who started the open-label study in a state of remission.

Summaries of adverse events were compiled for all patients using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* (COSTART).[21] Since the adverse event profiles for olanzapine and olanzapine-fluoxetine combination are very similar,[13] safety measures were analyzed for all patients (N = 562) who entered the open-label study, including those who discontinued from the acute-phase early, to increase the likelihood of detecting a potential safety signal.

RESULTS

Patients

Of the 379 patients who completed the acute study, 376 patients entered the 24-week extension study. Shown in Table 1 are the demographics and characteristics for patients who were included in this study. Patient data were

Table 1. Demographic and Illness Characteristics at End of Acute Phase

Characteristic	Remitters (N = 198)	Nonremitters (N = 178)
Age, mean (SD), y	41.3 (13.1)	44.2 (12.6)
Female, %	62.1	65.2
White, %	71.2	91.0
Body mass index, mean (SD)	28.4 (6.6)	30.5 (6.2)
Age at onset of bipolar disorder, mean (SD), y	24.1 (12.0)	26.3 (12.1)
MADRS baseline score, mean (SD)	6.1 (4.0)	22.2 (7.5)
CGI-BP baseline score, mean (SD)	2.0 (1.0)	4.0 (1.2)
YMRS baseline score, mean (SD)	2.0 (2.6)	4.2 (3.9)
Psychotic features, %	10.6	9.0
Melancholic features, %	66.2	64.6
Atypical features, %	6.6	7.3
Rapid-cycling course, %	30.3	36.0

Abbreviations: CGI-BP = Clinical Global Impressions scale-Bipolar Disorder version, MADRS = Montgomery-Asberg Depression Rating Scale, YMRS = Young Mania Rating Scale.

segregated according to symptomatic status at the last visit of the double-blind acute phase.

Among patients who entered the open-label extension study in remission, 35 had received olanzapine-fluoxetine combination, 96 olanzapine monotherapy, and 67 placebo in the acute study. The mean ± SD MADRS and CGI-BP scores for patients who started the study in remission were 6.1 ± 4.0 and 2.0 ± 1.0, respectively. For patients who entered the study in nonremission, the mean MADRS and CGI-BP scores were 22.2 ± 7.5 and 4.0 ± 1.2, respectively. Of those patients, 21 had received olanzapine-fluoxetine combination, 82 had received olanzapine monotherapy, and 75 had received placebo in the acute study.

The mean modal drug dose for the olanzapine monotherapy group was 8.3 mg/day. For the olanzapine-fluoxetine combination group, the mean modal drug dose was 8.1 mg/day for olanzapine and 41.9 mg/day for fluoxetine.

Treatment Response

Montgomery-Asberg Depression Rating Scale. Figure 2 shows mean MADRS scores during the 24-week open-label extension study for patients who entered in remission (left) or nonremission (right). Mean ± SD MADRS total scores at week 1, the first visit at which patients and physicians were given the option to switch treatments, were higher for those started in remission, changed treatment to olanzapine-fluoxetine combination, and stayed with this treatment for the remainder of the study relative to those who stayed with olanzapine monotherapy throughout the trial and to those who switched after week 1 (olanzapine-fluoxetine combination 8.3 ± 3.2 vs. olanzapine 3.4 ± 3.3, $p < .001$; olanzapine-fluoxetine combination vs. switched, 5.4 ± 4.0; $p = .001$). Mean MADRS total scores for patients who switched treatments after week 1 increased significantly from week 1 at all subsequent timepoints ($p < .05$). Among patients who entered the open-label study in remission, MADRS total scores did not change significantly from baseline to endpoint for the olanzapine-fluoxetine combination (0.8 ± SE 1.2, $p = .50$) and olanzapine (0.3 ± SE 0.8, $p = .73$) groups, but increased slightly in the switched group (2.3 ± SE 1.0, $p = .02$). Patients who entered the open-label phase in nonremission and received olanzapine-fluoxetine combination, olanzapine monotherapy, or switched treatments experienced significant baseline to endpoint decreases in MADRS total scores (–5.7 ± SE 1.7, $p = .001$; –11.6 ± SE 3.9, $p = .004$, and –6.4 ± SE 2.6, $p = .015$, respectively).

Clinical Global Impressions-Bipolar Severity Scale. Table 2 summarizes the mean baseline to endpoint changes in CGI-BP overall and CGI-depression and -mania subscores. Mean CGI-BP scores for patients in the olanzapine-fluoxetine combination group were significantly higher than those in the olanzapine group at week 1, the first visit at which patients were able to change treatments (olanzapine-fluoxetine combination: 2.4 ± 0.8, olanzapine: 1.7 ± 1.0; $p < .001$). Overall CGI-BP scores for patients who started in remission did not change significantly between baseline and endpoint for any of the treatment groups (olanzapine-fluoxetine combination: –0.3 ± 1.3, olanzapine: +0.1 ± 1.1, switched: 0.4 ± 1.4, NS). On the depression subscale of the CGI, scores for patients who entered the study in remission and received olanzapine-fluoxetine combination treatment decreased significantly from baseline to endpoint (–0.5 ±1.2, $p = .01$).

In patients who entered the open-label study in nonremission, overall CGI-BP scores decreased significantly from baseline to endpoint in all treatment groups (olanzapine-fluoxetine combination: –0.9 ± 1.4, $p < .001$; olanzapine: –0.9 ± 1.1, $p = .004$; switched: –0.6 ± 1.4, $p = .005$). Likewise, on the depression subscale of the CGI, scores decreased significantly for all treatment groups (olanzapine-fluoxetine combination: –0.9 ± 1.6, $p < .001$; olanzapine: –1.1 ± 1.1, $p = .002$; switched –0.6 ± 1.6, $p = .02$).

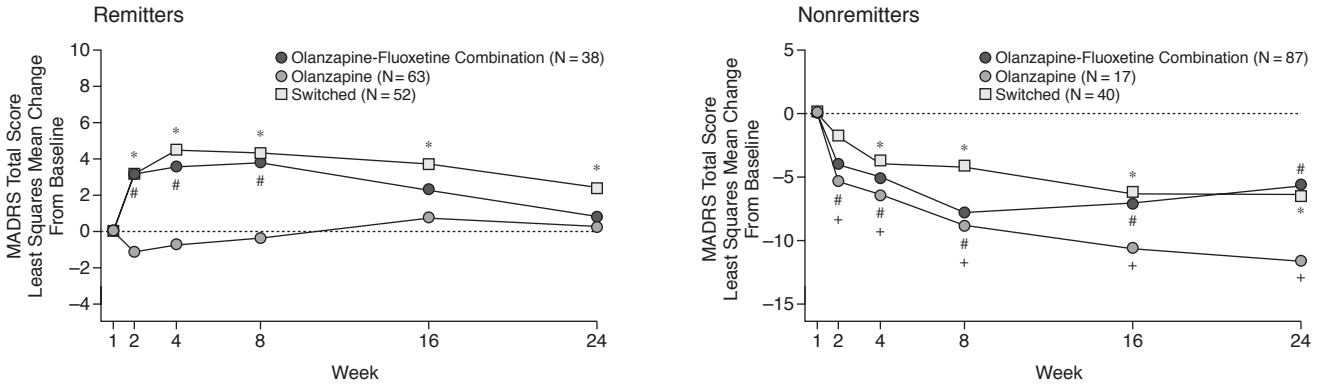
Remission

A majority of patients who started the trial in nonremission subsequently met remission criteria, as defined by a total MADRS score ≤ 12, at some point during the study (olanzapine-fluoxetine combination: 66.7% [58/87], olanzapine: 64.7% [11/17], switched: 62.5% [25/40]). Figure 3 shows the time to achieve remission of depressive symptoms for patients who entered the open-label extension in nonremission. The median times to meet remission criteria were as follows: olanzapine-fluoxetine combination: 48 days, olanzapine: 49 days, switched: 53 days.

Treatment-Emergent Mania

Mean YMRS scores at week 1 were not significantly different for patients in the olanzapine-fluoxetine

Figure 2. MMRM Analyses of Visit-Wise Changes From Baseline in MADRS Total Scores for Patients Who Entered the Open-Label Study in Remission (left) or Nonremission (right)[a]



[a]Significantly ($p < .05$) different from MADRS total score at week 1 for: # denotes olanzapine-fluoxetine combination; + denotes olanzapine; * denotes switched.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects model repeated-measures.

Table 2. Mean (SD) Changes in Clinical Global Impressions (CGI) Scores From Week 1 to Endpoint in the 24-Week Open-Label Extension Study

	Remitters (N = 153)[a]			Nonremitters (N = 144)[a]		
Assessment	Olanzapine-Fluoxetine Combination (N = 38)	Olanzapine (N = 63)	Switched (N = 52)	Olanzapine-Fluoxetine Combination (N = 87)	Olanzapine (N = 17)	Switched (N = 40)
CGI-bipolar	–0.3 (1.3)	0.1 (1.1)	0.4 (1.4)	–0.9 (1.4)*	–0.9 (1.1)*	–0.6 (1.4)*
CGI-depression	–0.5 (1.2)*	0.1 (1.1)	0.3 (1.5)	–0.9 (1.6)*	–1.1 (1.1)*	–0.6 (1.6)*
CGI-mania	0.1 (0.7)	0.2 (0.7)	0.1 (0.8)	0.1 (0.9)	0.0 (1.2)	–0.2 (1.0)

[a]Patient numbers differ from those at baseline due to loss of patient participation or change in remission status prior to the first visit in the open-label phase.
*Significant change from week 1 to endpoint, $p < .05$.
Abbreviation: CGI = Clinical Global Impressions scale.

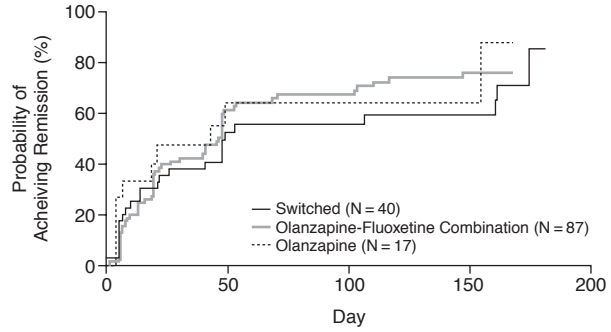
combination group relative to those in the olanzapine group, irrespective of remission status (remission: olanzapine-fluoxetine combination, 1.7 ± 2.0; olanzapine, 1.4 ± 2.4; nonremission: olanzapine-fluoxetine combination, 3.5 ± 3.2; olanzapine, 4.1 ± 5.0). YMRS scores did not change significantly from baseline to endpoint for patients who entered the study in remission (olanzapine-fluoxetine combination: 1.3 ± 5.3, olanzapine: 1.0 ± 5.4, switched: 0.6 ± 4.9, all NS). For patients who entered the open-label phase in nonremission, YMRS scores did not change significantly from baseline to endpoint with either olanzapine-fluoxetine combination (0.8 ± 5.5, NS) or olanzapine monotherapy (–0.7 ± 7.2, NS), but decreased in the group that switched treatments (–1.1 ± 4.9, $p = .02$).

Treatment-emergent mania was defined as a YMRS score < 15 at baseline and ≥ 15 at any time thereafter. The proportions of patients who started the open-label extension in remission and subsequently experienced treatment-emergent mania were as follows: olanzapine-fluoxetine combination, 3.4% (2/58); olanzapine, 4.5% (3/66); switched, 9.7% (6/62). For patients who started in nonremission, the proportions who experienced treatment-emergent mania were as follows: olanzapine-fluoxetine combination, 6.4% (6/94); olanzapine, 3.8% (1/26); switched, 6.3% (3/48).

Depressive Relapse

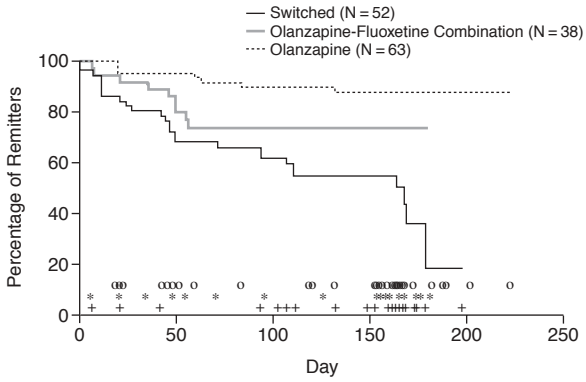
Relapse to a depressive episode was defined as a MADRS total score ≤ 12 at week 1 (remitters) and ≥ 16 at any time thereafter. The overall rate of relapse over the 6-month period was 27.4% (42/153). The proportions of depressive relapse, analyzed according to treatment course, were 23.7% (9/38) for those who switched and subsequently stayed with olanzapine-fluoxetine combination from week 1, 11.1% (7/63) for those who stayed with olanzapine, and 50% (26/52) for those who switched between treatments after week 1. Figure 4 depicts the time to relapse to a depressive episode during the open-label extension study and instances of censoring when patients discontinued participation in the study. Of the total number of patients who experienced depressive relapse at some point during the open-label period, 17 (40.5%) discontinued from the trial at the point of relapse, while the remaining 25 patients completed the trial. Of those 25 patients, 22 (88.0%) subsequently completed the trial in remission.

Figure 3. Time to Remission (MADRS ≤ 12) in Patients Who Entered the Open-Label Extension Study in Nonremission (MADRS score ≥ 12)



Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Figure 4. Time to Depressive Relapse (MADRS score ≥ 16) for Bipolar Disorder Patients Who Started the 24-Week Open-Label Trial in Remission (MADRS score ≤ 12)



o denotes censored patients for olanzapine.
* denotes censored patients for olanzapine-fluoxetine combination.
+ denotes censored patients for switched.
Abbreviation: MADRS = Montgomery-Asberg Depression Rating Scale.

Safety and Tolerability

Rates of study completion and reasons for discontinuation are reported in Table 3. Adverse events that emerged during the study or that were present at baseline, but worsened in severity, were considered treatment emergent. Safety measures were analyzed for all patients (N = 562) who entered the open-label study and had determinations at both baseline and postbaseline visits, including those who discontinued from the acute-phase early. A summary of unsolicited adverse events reported by 5% or more patients is provided in Table 4. A significant baseline to endpoint increase in mean body weight (2.6 ± 5.1 kg, $p < .001$) was observed. Supine systolic blood pressure increased significantly from baseline to endpoint (1.5 ± 14.4 mm Hg, $p = .02$). Mean nonfasting glucose values increased significantly from baseline (103.5 ± 38.88 mg/dL) to endpoint by 3.06 ± 29.7 mg/dL, $p = .02$. The incidence of treatment-emergent glucose elevation, defined as ≥ 200 mg/dL, was 2.5% (13/511). Mean nonfasting total cholesterol increased significantly from baseline (210.14 ± 47.60 mg/dL) to endpoint by 12.00 ± 39.47 mg/dL, $p < .001$. The incidence of treatment-emergent changes in nonfasting total cholesterol, defined as ≥ 240 mg/dL, was 3.9% (7/178).

Two deaths due to suicide occurred during the open-label study. Both patients received olanzapine monotherapy during the open-label period. Based on the investigator's opinion, neither of these events was related to study drug. No significant changes in extrapyramidal symptoms were observed during the open-label period, as assessed with the AIMS and Simpson-Angus scales.

DISCUSSION

In this open-label extension study, treatment with olanzapine-fluoxetine combination or olanzapine monotherapy was associated with sustained therapeutic response in patients with bipolar I disorder who previously achieved remission from an acute depressive episode. This is reflected in the mean MADRS scores, which remained stable from baseline to endpoint of the 24-week study. Furthermore, in this subset of remitted patients, those who received treatment with olanzapine-fluoxetine combination showed qualitative improvements in residual symptoms as indicated by significant decreases in scores on the CGI-BP depression subscale.

Among patients who started the open-label phase in remission, an overall depressive relapse rate of 27% was observed, which indicates that not all patients remained well during the 24 weeks of the study. Given the paucity of data regarding long-term efficacy of treatments for bipolar depression, it is difficult to place these relapse rates in context. In a placebo-controlled 18-month trial of lamotrigine and lithium for maintenance treatment in recently depressed patients with bipolar I disorder, the proportions of patients requiring intervention for depression at 1 year were 55%, 54%, and 43% for placebo, lithium, and lamotrigine, respectively.[22] The findings suggest that recently depressed patients with bipolar I disorder may be more refractory to treatment and experience depressive relapse more frequently (relative to recently manic patients).[23] Moreover, in a longitudinal study of bipolar I disorder, patients spent a greater proportion of time with depressive symptoms relative to manic symptoms.[3]

Long-term treatment with olanzapine-fluoxetine combination or olanzapine monotherapy was associated with a low rate of treatment-emergent mania among patients who entered the extension study in remission. In this patient population, the overall incidence of manic episodes

Table 3. Patient Disposition

Assessment	Remitters (N = 198)			Nonremitters (N = 178)		
	Olanzapine-Fluoxetine Combination (N = 59)[a]	Olanzapine (N = 70)[a]	Switched (N = 62)[a]	Olanzapine-Fluoxetine Combination (N = 95)[a]	Olanzapine (N = 30)[a]	Switched (N = 50)[a]
Completed study, N (%)	32 (54.2)	49 (70.0)	41 (66.1)	54 (56.8)	17 (56.7)	24 (48.0)
Discontinued treatment, N (%)	27 (45.8)	21 (30.0)	21 (33.9)	41 (43.2)	13 (43.3)	26 (52.0)
Adverse events	5 (8.5)	5 (7.1)	2 (3.2)	9 (9.5)	4 (13.3)	7 (14.0)
Lack of efficacy	5 (8.5)	0 (0)	3 (4.8)	15 (15.8)	0 (0)	6 (12.0)
Lost to follow-up	6 (10.2)	4 (5.7)	5 (8.1)	4 (4.2)	3 (10.0)	7 (14.0)
Emergence of mania	2 (3.4)	1 (1.4)	1 (1.6)	2 (2.1)	2 (6.7)	1 (2.0)
Relapse to depression	3 (5.1)	2 (2.9)	3 (4.8)	4 (4.2)	1 (3.3)	1 (2.0)
Other reasons	6 (10.2)	9 (12.9)	7 (11.3)	7 (7.4)	2 (6.7)	4 (8.0)
Death[b]	0 (0)	0 (0)	0 (0)	0 (0)	1 (3.3)	0 (0)

[a]Patient numbers differ from those at baseline due to the loss of patient participation prior to the first visit in the open-label phase.
[b]One death due to suicide occurred before the first scheduled visit and is not listed in this table because treatment course could not be defined.

Table 4. Summary of Drug-Related Adverse Events (≥ 5%) From a 24-Week Open-Label Extension Study of Olanzapine-Fluoxetine Combination or Olanzapine Monotherapy for Treatment of Bipolar Depression

Adverse Event, N (%)	Olanzapine (N = 100)[a]	Olanzapine-Fluoxetine Combination (N = 154)[b]
Weight gain	17 (17.0)	25 (16.2)
Somnolence	9 (9.0)	18 (11.7)
Depression	9 (9.0)	18 (11.7)
Rhinitis	7 (7.0)	11 (7.1)
Anxiety	7 (7.0)	11 (7.1)
Insomnia	9 (9.0)	6 (3.9)
Manic reaction	6 (6.0)	8 (5.2)
Headache	8 (8.0)	5 (3.3)
Increased appetite	5 (5.0)	8 (5.2)
Asthenia	3 (3.0)	8 (5.2)
Back pain	2 (2.0)	8 (5.2)
Constipation	5 (5.0)	5 (3.3)
Nervousness	2 (2.0)	8 (5.2)
Urinary tract infection	6 (6.0)	4 (2.6)

[a]Patients who received olanzapine only during the open-label phase.
[b]Patients who received olanzapine-fluoxetine combination only after week 1 in the open-label phase.

across all treatment groups was low (5.9%), and mean YMRS scores remained stable over the course of the 6-month study. Similarly, the rate of treatment-emergent mania among patients who entered the study in nonremission was 6.0%. These findings are notable in light of the fact that 80.7% of patients who entered the acute study reported experiencing a manic or mixed episode within the prior 12 months.[14]

The continuing controversy over risks associated with antidepressant treatment and potential induction of mood instability in patients with bipolar depression has been recently reviewed.[24,25] Induction of manic episodes or cycle acceleration is considered to have negative consequences on illness progression and is associated with diminished responsiveness to subsequent treatments. However, this risk should be weighed against the prophylactic value of long-term antidepressant treatment in conjunction with a mood stabilizer to diminish the risk of relapse to a depressive episode. This point has been highlighted in a recent report by Altshuler et al.[26] in which higher rates of depressive relapse were observed in a patient population that discontinued antidepressant treatment as an adjunct to a mood stabilizer relative to a population that continued adjunctive treatment with an antidepressant. Notably, continued adjunctive treatment with antidepressants did not appear to increase the risk for manic relapse. However, these findings do not rule out the possibility that various classes of antidepressant drugs may be associated with differential risks of mania induction. For example, treatment with tricyclic antidepressants, and more recently venlafaxine, has been associated with higher risk of mania induction relative to SSRIs and bupropion.[12,25,27,28] The current study did not have a fluoxetine monotherapy arm; thus the risk of mania reduction relative to olanzapine-fluoxetine combination or olanzapine monotherapy can not be determined.

The design of the present study precludes meaningful comparisons between treatment courses with regard to efficacy in the control of depressive symptoms, relapse prevention, or emergence of mania. This is due, in part, to the open-label, flexible course of treatment available to the patients. As specified in the study protocol, patients and physicians were given the option to change treatments after week 1 and at subsequent visits when a deterioration of condition was judged during clinical evaluation. Thus, patient distribution in the different treatment courses was determined partly by the direction of illness progression during the interval preceding each evaluation. Some degree of treatment self-selection may be reflected in the significantly higher mean MADRS score at week 1 for patients who entered the open-label phase in remission and changed to olanzapine-fluoxetine combination, relative to those who stayed with olanzapine monotherapy. Thus, the olanzapine-fluoxetine combination and switched treatment groups may have comprised patients whose mood symptoms were more difficult to control, irrespective of treatment. This is further borne out by the observation that patients who switched treatments after week 1 experienced a higher incidence of depressive

relapse relative to the other treatment groups. Despite findings at week 1, mean MADRS scores at endpoint for patients in the switched group were not significantly different from baseline. Furthermore, more than half of the patients in the switched group who experienced depressive relapse completed the study and were in remission at endpoint.

The second subset of patients examined in this study consisted of those who completed the acute phase but did not achieve remission at endpoint. The mean MADRS score for patients in this group at the outset of the open-label phase was 22.2, which would be considered moderately severe depression. Among these patients, a majority (65.3%) subsequently achieved remission criteria (MADRS total score ≤ 12). This finding is reflected in the significant baseline-to-endpoint decreases in MADRS scores for patients in all treatment groups. Similar decreases were seen in all treatment groups on the CGI-BP and CGI-depression scales. A portion of these effects on depressive symptoms may be attributed to the start of medication in patients who had received placebo in the preceding acute phase trial. However, this subset of patients constituted only 38.2% of patients who started the open-label phase in nonremission, and of the previous placebo-treated patients, 65.6% achieved remission. Thus, continued treatment with olanzapine-fluoxetine combination or olanzapine monotherapy may have contributed to the control of depressive symptoms in patients who had not initially responded to a shorter course of treatment in the preceding 8-week trial. Given the same treatment self-selection bias described earlier, it is interesting to note that, in the population of patients who started in nonremission, 88.2% chose to change treatment to olanzapine-fluoxetine combination at some point during the trial, and 60.4% changed at the first opportunity (week 1) and stayed with the treatment throughout. Also notable in this subset of patients was the low overall rate of treatment-emergent mania, which did not differ among the treatment groups.

The present study used an open-label design, and the findings should be considered within the limitations associated with unblinded, nonrandomized treatment. There are several aspects of the study design that warrant additional consideration. First, all patients who entered the open-label extension study were required to complete 1 week of open-label treatment with olanzapine monotherapy (5–10 mg/day). Therefore, patients who were retrospectively ascribed to the olanzapine-fluoxetine combination group also received an initial week of olanzapine monotherapy. Second, treatment could be switched at any visit between olanzapine-fluoxetine combination or olanzapine monotherapy; therefore, bias introduced by treatment self-selection may have influenced outcomes. Third, the current study involved a partially enriched population of patients of which approximately 62% had received olanzapine monotherapy or olanzapine-fluoxetine combination during the 8-week acute phase. Thus, patients who were either nonresponsive to or intolerant of either treatment may have been excluded from the open-label study, making generalizations regarding efficacy or adverse event rates to a broader population difficult.

Open-label treatment with olanzapine-fluoxetine combination or olanzapine monotherapy appeared to be well tolerated in this study, with 52.3% of patients completing the 6-month trial. Rates of discontinuation due to adverse events were 6.3% for remitters and 11.4% for nonremitters. Rates of discontinuation due to lack of efficacy were 4.2% for remitters and 12.0% for nonremitters. In terms of safety, the adverse event profile of olanzapine during the open-label phase of the trial was consistent with findings from the acute-phase trial,[14] and with other long-term studies in patients with bipolar disorder.[29,30] The adverse event profile of olanzapine-fluoxetine combination was similar to that of olanzapine. During the 6-month study period a significant increase in mean body weight was observed, as well as significant baseline to endpoint increases in mean nonfasting glucose and nonfasting cholesterol levels. These findings are also consistent with previous reports from long-term studies with olanzapine.[29,30] The present findings and those from the preceding acute phase study suggest that clinicians should continue to evaluate the benefits associated with treating depressive symptoms and maintaining mood stability against the potential risks associated with weight gain over the course of long-term management of bipolar depression.

In summary, the findings of this 6-month open-label study indicate that the olanzapine-fluoxetine combination was well-tolerated in patients with bipolar depression. Longer term treatment with the olanzapine-fluoxetine combination was not associated with an increased risk of treatment-emergent mania. Although controlled studies are needed to characterize the relative value of longer term treatment with olanzapine-fluoxetine combination versus olanzapine monotherapy after initial treatment of bipolar depression, findings from the present study suggest that there may be therapeutic benefits to extending combination antidepressant treatment beyond the management of acute depressive episodes. As discussed in a recent systematic review by Gijsman et al.,[25] these results contribute to a knowledge database that is sorely in need of data from long-term assessments of management for bipolar depression with respect to both the treatment of depressive symptoms and the maintenance of mood stability.

Drug names: benztropine (Cogentin and others), biperiden (Akineton), bupropion (Wellbutrin and others), fluoxetine (Prozac and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), lorazepam (Ativan and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), venlafaxine (Effexor).

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